Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review article

Acute disseminated encephalomyelitis (ADEM) following COVID-19 vaccination: A systematic review

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ABSTRACT

Background: Although global vaccination against COVID-19 infection has its excellence, potential side effects are yet of concern. Several lines of evidence have proposed ADEM occurrence after SARS-CoV-2 infection. Moreover, a large number of case reports and case series have also suggested the casual association between ADEM and COVID-19 vaccination. To better understand the development of ADEM following COVID-19 vaccination and its potential association, we aimed to systematically review ADEM cases reported after COVID-19 vaccination.
Methods: We conducted a comprehensive systematic search using three databases including PubMed, Scopus, and Web of Science. Studies that reported ADEM after COVID-19 vaccination were eligible to include in our study. Observational studies, case reports, and case series which reported cases of ADEM with sufficient detail to confirm clinical diagnosis following COVID-19 vaccination were eligible to enter our study.
Results: Twenty studies were included in our systematic review after the abstract and full-text screening with a total of 54 cases. Among included patients, 45 (85.1 %) developed ADEM after the first dose of the COVID-19 vaccine, and seven (12.9 %) cases experienced ADEM after the second dose. The median time interval between vaccination and neurological symptoms was 14 days which ranged from 12 h to 63 days. Twelve (22.2 %) patients experienced symptoms of muscle weakness, ten (18.5 %) presented unconsciousness, nine (16.6 %) patients had urinary complaints, nine (16.6 %) had visual impairments, and five (9.2 %) experienced a seizure. After treatments, four (13.8 %) patients died. Forty-six patients had clinical improvement (85.1 %), also improvement in brain MRI was observed among 44 (81.4 %) patients.
Conclusion: In conclusion, it is not clear that ADEM could be a potential complication of COVID-19 vaccination based on the current evidence and further studies are needed. However, this rare condition should not trigger stopping the mass vaccination programs since the only way to eradicate the current pandemic of COVID-19 is to extend the number of immunized people.

1. Introduction

The coronavirus disease 19 (COVID-19) pandemic caused by the severe respiratory syndrome coronavirus 2 (SARS-CoV-2) was first presented in Wuhan, China, 2019 [1]. With the rapid development of vaccines, substantial protection against COVID-19 was provided [2,3]. So far, 65.5 % of the world population has been efficaciously immunized with at least one dose of the COVID-19 vaccines to date [1,4]. The most common worldwide administered vaccine types were Messenger RNA (mRNA) vaccines, including Pfizer/BioNTech (BNT162B2) and Moderna (mRNA-1273), alongside viral vector vaccine Oxford/AstraZeneca (ChAdOx1), respectively [5]. Although global vaccination against COVID-19 infection has its excellence, potential side effects are yet of concern. Along with general side effects reported after the COVID-19 vaccination such as fever, fatigue, and myalgia, some rare but severe neurological complications have also been recognized including cerebral venous sinus thrombosis (CVST), Guillain Barre Syndrome (GBS) and central nervous system (CNS) demyelination disorders [2,6–8].

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Acute disseminated encephalomyelitis (ADEM) is a rare autoimmune disease mostly occurring in children and young adults [9,10]. It is well known for its acute-onset and rapidly progressive demyelinating process both in the brain and spinal cord [11]. Although the exact underlying mechanism of ADEM is still a matter of discussion, it is suggested that ADEM mainly occurs after bacterial and viral infection alongside vaccination [12–14]. Several studies have reported ADEM occurrence after SARS-CoV-2 infection [15–17]. Moreover, a large number of case reports and case series have also suggested the potential association between ADEM and COVID-19 vaccination [18–23].

To better understand the development of ADEM following COVID-19 vaccination and its potential association, we aimed to systematically review ADEM cases reported after COVID-19 vaccination. Together, this systematic review study hopefully yields insights into post-COVID-19-vaccination presentations of ADEM and how it differs from the typical ADEM manifestations with the final purpose of early detection and efficient management of those at risk.

2. Methods and materials

We followed the preferred reporting items for systematic reviews and *meta*-analyses (PRISMA) guidelines for the present systematic review [24].

2.1. Literature search

We conducted a comprehensive systematic search using three databases including PubMed, Scopus, and Web of Science. The following terms were used in our search strategy: ((Acute Disseminated Encephalomyelitis) or (ADEM)) and (COVID-19 or SARS-COV-2 or coronavirus or Coronavirus Disease or 2019-nCoV Disease) and (Vaccination or Vaccine or immunization). Additionally, we manually searched the reference list of review studies to identify relevant studies.

2.2. Eligibility criteria

Observational studies, case reports, and case series which reported cases of ADEM with sufficient detail to confirm clinical diagnosis following COVID-19 vaccination were eligible to enter our study. Review and non-English studies were excluded. Also, studies reported patients with prior history of any demyelinating disease were excluded.

2.3. Study selection

Two independent investigators (SH.R, F.N) screened the title and abstract of the studies and excluded non-relevant papers. Next, the remained studies underwent full-text evaluation for final selection. Any disagreements were resolved by consultation with the third investigator.

2.4. Data extraction

The following information was extracted for each case by the two reviewers (SH.R, F.N) using a prepared datasheet: Study demographic, age, sex, neurological symptoms, type of COVID-19 vaccine, dosage, the time interval between vaccination and neurological symptoms, MRI results, CSF findings, auto-antibodies results, SARS-CoV-2 PCR results, treatments, and Outcome.

2.5. Quality assessments

We used Joanna Briggs Institute Critical Appraisal tools to assess the quality of case series and case report studies which contains eight questions with answers based on “Yes” or “No” and a total score of 0 to 8[25].

3. Results

A total of 159 studies were retrieved from the databases after duplicate removal (Fig. 1). Next, 88 studies were excluded via title and

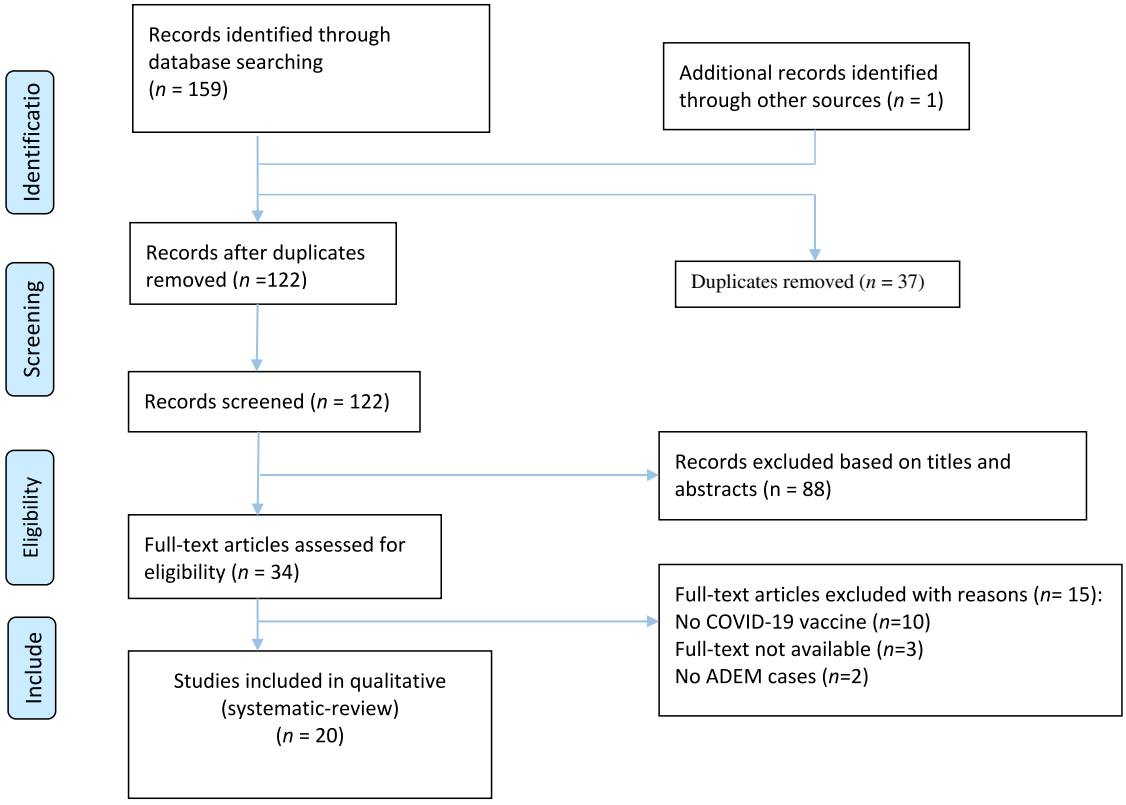

Fig. 1. PRISMA flow diagram depicting the flow of information through the different phases of a systematic review.

Table 1
Characteristics and clinical findings of inlcuded studies.

First author	Country	Age	Sex	Neurological symptoms	Type of COVID-19 vaccine	Dosage of COVID-19 vaccine	Time interval between vaccination and neurological symptoms	MRI results	CSF findings	Auto-antibodies	SARS-CoV-2 PCR	Treatment	Outcome
Al-Quliti et al. 2022	Saudi Arabia	56	Female	Gradual discomfort + generalized weakness + myalgias + difficultly in the articulation of speech + needed assistance to ambulate + anorexia + dysmetria	AstraZeneca (ChAdOx1)	1st	10d	MRI: the T2 and FLAIR sequences demonstrated large multifocal, bilateral, asymmetric, multiple hyperintensities in the subcortical and deep white matter involving the basal ganglia with no contrast enhancement	CSF: protein = 1.76, CSF glucose = 4.62; CSF WBC count = 1, RBC count = 7; (CSF differential cells) CSF segs = 20 %, CSF mono = 64 %, lymphocytes = 16 %	NR	Negative	Omeprazole + acetaminophen + hypertonic saline at 2 % + sodium correction over the next 24 h + MPS + physical and occupational therapy	Complete resolution of her symptoms, continued to improve and was able to mobilize freely without assistance, discharged from hospital
Ancau et al. 2021	Germany	61	Male	Fever + headache + apathy + unconscious + foaming around the mouth + generalized seizure + comatose	AstraZeneca (ChAdOx1)	1st	2d	MRI: bilateral confluent cortical and subcortical FLAIR hyperintense lesions with hemorrhagic involvement of the basal ganglia	CSF: normal cell counts (1 leukocyte per μl) and moderate disturbance of the blood–brain-barrier + No CSF-specific oligoclonal bands or intrathecal IgG/-A/-M−synthesis were detected	against aquaporin-4 (AQP4) or myelin oligodendroyte glycoprotein (MOG) in cell-based assays (CBA) = negative + Screening for antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA), antiphospholipid antibodies, neuronal and paraneoplastic antibodies = all negative.	Negative	Endotracheal intubation + MPS + PE	Slight improvement, reduction in size of the brain lesions, on clinical follow-up after 14 weeks of rehabilitation, the patient presented with a vegetative state
		25	Female	Severe cephalgia + thoracic back pain + mild weakness + ascending numbness + complete paraplegic syndrome	AstraZeneca (ChAdOx1)	1st	9d	Spinal MRI: a longitudinal edema throughout the thoracic spinal cord exhibiting mild contrast enhancement as well as focal central hemorrhages + Cranial MRI: bi-hemispheric white matter lesions with focal contrast enhancement	CSF: erythrocytes 5,284 cells/μl, leukocytes241 cells/μl + highly elevated CSF/serum quotient for albumin of 164.7 × 10–3 + No CSF-specific oligoclonal bands were detected	Intrathecal IgM synthesis = positive, but IgG or IgA synthesis = negative / glial-, neuronal-targeting, and paraneoplastic autoantibodies (CBA for AQP4- and MOG-, immunofluorescence assays in the serum for ANA, ANCA, anti-double stranded DNA antibodies) = negative	Negative	MPS + PE	Cephalgia improved drastically and the sensory components slightly, clinical improvement of only sensory symptoms
		55	Female	Progressive nausea + dizziness + meningism + severe spastic tetraparesis + increased intracerebral pressures +	AstraZeneca (ChAdOx1)	1st	9d	Brain MRI: multiple FLAIR-hyperintense and hemorrhagic lesions in the right parietal and temporal lobes, bilaterally in fronto-temporal distribution as well as in the right occipital	CSF: mixed granulocytic and lymphocytic pleocytosis (10/μl) and a normal CSF/serum quotient for albumin of 7.4 × 10–3 + No CSF-specific oligoclonal bands were detected	Intrathecal IgM, IgA and IgG synthesis = positive / Both autoimmune (AQP4-, MOG-autoantibodies as measured by CBA), and paraneoplastic antibodies (immunofluorescence	Negative	emergency right-sided decompressive hemicraniectomy + MPS	Significant improvement of vigilance and motor function, died (due to progressive intracerebral hemorrhage of the brain stem)

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Table 1 (*continued*)

First author	Country	Age	Sex	Neurological symptoms	Type of COVID-19 vaccine	Dosage of COVID-19 vaccine	Time interval between vaccination and neurological symptoms	MRI results	CSF findings	Auto-antibodies	SARS-CoV-2 PCR	Treatment	Outcome
				comatose + anisocoria				lobe and left fronto-basal region		assays in the serum) = negative			
Ballout et al. 2022	USA	81	Male	Change in mental status + severe encephalopathy + viral-like illness + fever + fatigue + myalgia + acute inflammatory demyelinating process	Moderna	1st	13d	Brain MRI with gadolinium: on hospital Day 5 a diffusion restricting lesion involving the right dorsal medulla with corresponding T2 FlAIR hyperintensity, very faint left pontine, midbrain, and thalamic T2 FlAIR hyperintensity, and minimal T2 sulcal hyperintensity without apparent enhancement suggestive of a possible inflammatory or infectious process / Repeated Brain MRI with gadolinium: on hospital day 17 demonstrated multiple, non-enhancing, T2 hyperintense lesions involving bilateral frontoparietal lobes, lentiform nuclei, thalami, cerebral peduncles, pons, and right posterior medulla	1st CSF: opening pressure = 26 cmH2O, glucose = 69 mg/dL (reference range 40–70 mg/dL), protein = 45 mg/dL (reference range 15–45 mg/dL), and WBC count = 3 cells/μL (reference range 0–5 cells/μL). / 2nd CSF: a mild lymphocytic pleocytosis with a WBC count of 11 cells/μL and protein of 52 mg/dL / A CSF autoimmune encephalitis panel + negative / 3rd CSF: pleocytosis of 69 cells/μL with 83 % lymphocytic predominance, protein of 45 mg/dL, and significantly elevated myelin basic protein (MBP) > 167.0 ng/mL (reference range 0–6.0 ng/mL).	anti-MOG antibody = negative	Negative	Vancomycin + IVIG + MPS + PE	Died (due to hemorrhagic shock of probable gastrointestinal origin)
Francis et al. 2022	UK	36 median	14 Female	Transeverse myelitis + optic neuritis + Fever + Headache + dysesthesia + Posterma + Facial nerve palsy + paraplegia	18 AstraZeneca (ChAdOx1) and 7 Pfizer (BioNTech)	23 at 1st and two at 2nd	20d	Brain MRI: Involving cerebrall peduncles, internal capsule, splenium, and spinal cord. Longitudinally extensive transverse myletis and **periependymal FLAIR hyperintensities.**	CSF: Protein (0.63 g/L, range 0.33–2.25), lymphocyte count was 36 × 106/L, and negative oligoclonal bands (OCBs) in MOGIgG + Patients.	Twelve patients were MOGIgG + and two patients were AQP4IgG+	NR	IVMP + PE + IVIG	Only two patients had poor recovery
Ahmad et al. 2022	USA	61	Female	General weakness and difficulty in communications	Pfizer (BioNTech)	1st	63d	Brain MRI: Signficant diffuse and symmetric acute leukoencephalopathy process involving the deep white matter extending downward through the brainstem into the cerebellar white matter tracts	White blood cell count of 10.1 K/uL and hemoglobin of 12.6 g/dL. Her comprehensive metabolic panel was significant for potassium of 3.2 mmol/L, bicarbonate of 11 mmol/L, chloride of 120 mmol/L. Additional tests, including	Negative myelin oligodendrocyte glycoprotein (MOG)	Negative	MPS + IVIG	Significant improvement in the patient's mentation. There was no further disease progression in brain MRI

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Table 1 (*continued*)

First author	Country	Age	Sex	Neurological symptoms	Type of COVID-19 vaccine	Dosage of COVID-19 vaccine	Time interval between vaccination and neurological symptoms	MRI results	CSF findings	Auto-antibodies	SARS-CoV-2 PCR	Treatment	Outcome
									procalcitonin, cortisol, glucose level, thyroid function tests, antinuclear antibody screen, and COVID RNA nasopharyngeal swab, were within normal limits. Her urinalysis was unremarkable, but her urine toxicology was positive for tetrahydrocannabinol.				
Cao et al. 2021	China	24	Female	Somnolence + memory decline + headache + low-grade fever + muscle stiffness + extremity weakness + reduced appetite + generalized tonic–clonic seizure	Vero Cells	1st	2w (14d)	Brain MRI: abnormal signals in the bilateral temporal cortex / Repeat brain MRI: an increased number of lesions, which were more striking in appearance on day 10; the lesions were improved by day 15	1st CSF: WBC count = 51 × 106/L / 2nd CSF: WBC count = 25 × 106/L	anti-aquaporin-4, anti-myelin basic protein, anti-MOG, anti-glial fibrillary acidic protein, autoimmune encephalitis, and paraneoplastic syndrome = all negative	Negative	Ceftriaxone + acyclovir + diazepam + levetiracetam + IVIG	MMSE scores improved, discharged, on a visit 1 month after discharge, felt no discomfort, and a repeat MRI showed complete resolution of brain lesions
Kania et al. 2021	Poland	19	Female	Severe headache + fever + back and neck pain + nausea + vomiting + urinary retention + atopic dermatitis + depression + nuchal rigidity + bilateral Babinski signs	Moderna	1st	2w (14d)	Brain MRI: multiple, poorly demarcated, hyperintense lesions in T2-weighted and fluid-attenuated inversion recovery (FLAIR) images located in both brain hemispheres, pons, the medulla oblongata, and cerebellum. Few of them were contrast-enhanced lesions. Cervical and thoracic MRI revealed a widespread hyperintense area in T2-weighted and FLAIR images extended from medulla oblongata to Th11 segment with overlapping few contrast-enhancing lesions	CSF: WBC count = 294 × 106/L, lymphocytes = 91 %, monocytes = 8 %, neutrophils 1 %, protein levels = 648 mg/L, RBC count = 77/μL / Control lumbar puncture was done 12 days after the first one; CSF WBC count = 61 × 106/L and protein levels = 338 mg/L.	anti-aquaporin-4 and anti-myelin oligodendrocyte glycoprotein = negative	NR	Ceftriaxone + acyclovir + MPS + PE	The clinical status improved after MPS, discharged from the hospital without any symptoms except a mild headache
Kenangil et al. 2021	Turkey	46	Female	Tonic–clonic seizure	Sinovac	2nd	1 month (30d)	Cranial MRI: There were scattered hyperintense lesions in the left thalamus,	CSF: acellular with normal protein content (45 mm/dL), an IgG index of 0.64 + no oligoclonal bands	ANA (1/100) + anti-SOX1 antibody = positive / anti-double-stranded DNA and	Negative	Steroids	Controlled MRI, without any new signs, symptoms, or seizures.

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Table 1 (*continued*)

First author	Country	Age	Sex	Neurological symptoms	Type of COVID-19 vaccine	Dosage of COVID-19 vaccine	Time interval between vaccination and neurological symptoms	MRI results	CSF findings	Auto-antibodies	SARS-CoV-2 PCR	Treatment	Outcome
								bilateral corona radiata, left diencephalon, and right parietal cortex on T2 and FLAIR sequences on MRI. Some of these lesions showed mild restricted diffusion on DWI		extractable nuclear antigen (ENA) panel, anti-aquaporin-4 and anti-myelin oligodendrocyte (MOG) antibodies = negative			
Lazaro et al. 2022	Argentina	26	Female	Disorientation + inappropriate behavior + headache + gait imbalance + deferred memory + hypoprosexia + anosognosia + incoherent speech + visuospatial failures + Right upper limb weakness + gait ataxia	Sputnik	1st	4w (28d)	Brain MRI: nodular hyperintense lesions on T2-weighted image and fluid attenuated inversion recovery without restricted diffusion on diffusion. Marked vasogenic edema and T1-weighted image post contrast incomplete annular enhancement was observed	CSF: 3 cells, 50 g proteins/L, normal glucose + Oligoclonal bands (OCB) = positive / White blood cell count = 3–66 % mononuclear, Proteins = 50.6, Glucose = 78.3, Lactic acid = 1.74, Culture (bacterial, fungal and KOCH) = Negative, VDRL = Negative, Viral PCR (Herpes simplex I/I, Varicella Zoster, Cytomegalovirus, Epstein Barr, Enterovirus, Chagas, John Cunningham) = Negative, Mycobacterium Tuberculosis PCR = Negative, Oligoclonal Bands = Type 2	Anti-myelin oligodendrocyte glycoprotein antibody (anti-MOG) IGG = negative	NR	MPS	The clinical course was favourable, neurological examination was normal, the MRI was repeated after three months, showing clear imaging improvement of all the lesions
Maramattom et al. 2022	India	64	Male	Ascending paresthesias in the legs + epigastric band-like sensation + leg stiffness + hand paresthesias	AstraZeneca (ChAdOx1)	2nd	20d	Brain and spine MRI: bilateral corticospinal tract hyperintensities, Dorsal cord hyperintensity at D8–9, Whole-body PET/CT normal (multifocal cord hyperintensities and bilateral hemispheric corticospinal tract hyperintensities)	CSF: normal	NMDA/VKGC/NMO, MOG/paraneoplastic panel = negative	NR	IVIG + IVMP + rituximab	A repeat MRI at 1 month showed stabilization of the lesions and no new contrast enhancement (mRS 1 Level 2)
		46	Male	Urinary complaints + progressive lower limb weakness + numbness + fever	AstraZeneca (ChAdOx1)	1st	4d	Brain and spine MRI: extensive supratentorial + infratentorial + long segment spinal cord hyperintensities + longitudinally extensive transverse myelitis (MRI brain: T2, FLAIR hyperintensities in bilateral middle	CSF: 63 cells/mm3, Protein (52 mg/dl), sugar (93 mg/dl), CSF encephalitis panel: negative	Serum NMO, MOG, ANCA = negative	Negative	MPS + IVMP + PE	Improved significantly and was able to ambulate independently (Recovered, mRS 1 Level 2)

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Table 1 (*continued*)

First author	Country	Age	Sex	Neurological symptoms	Type of COVID-19 vaccine	Dosage of COVID-19 vaccine	Time interval between vaccination and neurological symptoms	MRI results	CSF findings	Auto-antibodies	SARS-CoV-2 PCR	Treatment	Outcome
								cerebellar peduncle (left > right), pontine tegmentum, right paramedian medulla, and left thalamocapsular region)					
		42	Female	Severe daily headache + photophobia + papilledema	AstraZeneca (ChAdOx1)	1st	5d	MRI: initial MRI: leptomeningeal and sulcal enhancement / 25 days later: large right temporal irregular enhancing lesion with significant perilesional edema	CSF: opening pressure 32 cm H2O, CSF parameters normal	Serum & CSF autoimmune encephalitis/NMO, MOG/viral encephalitis panel = all negative	NR	Decompression of lesion + Excisional biopsy + Oral prednisolone	Headache remitted spontaneously after the excision biopsy (mRS 1)
Miyamoto et al. 2022	Japan	54	Female	Fever + headache + somnolence + urinary retention + decreased level of consciousness	Pfizer (BioNTech)	2nd	12d	Brain MRI: lesions in the bilateral basal ganglia, midbrain, and cerebral white matter	CSF: elevated protein levels (31.2 mg/mL) + increased cell count (23/μL, 91 % mononuclear cells) + elevated myelin basic protein (809.8 pg/mL)	anti-aquaporine-4 antibody + other encephalitis-related auto-antibodies (glutamate receptors, leucine-rich glioma-inactivated protein 1, contactin-associated protein 2, and glial fibrillary acidic protein) = all negative	NR	MPS + PE + IVIG	Discharged and recovered, able to perform activities of daily living independently.
Mumoli et al. 2021	Italy	45	Male	Objective vertigo + fever + diffuse myalgia + feeling of burning on the back + backpain + (knees, thighs and perineum) numbness and hypoesthesia + urinary retention + loss of feet's vibration sensation + gait difficulties and febrile status	AstraZeneca (ChAdOx1)	1st	12 h (0.5d)	Spinal cord MRI: a central non expansive short tau iversion recovery (STIR) signal lesions extended to spinal cord from D10 until conus without enhancement after administration of gadolinium	CSF: 43 cells (cut off < 25) associated with mild hyperproteinorachia (406 mg/l; cut off 305) + normal glycorrhachia and oligoclonal bands	IgG = positive / Autoimmune screening = normal / Acquaporin-4 antibodies = negative / anti-MOG = positive with a titer 1:2560 (positive ≥ 1:160)	Negative	Ceftriaxone + piperacillin/tazobactam + MPS	Brain and Spinal cord status was improved, the hyperintense streak in STIR has almost completely disappeared, and Anti MOG titer was stable.
Nagaratnam et al. 2022	Australia	36	Female	Headache + photophobia + blurred vision + bilateral visual impairment + subjective colour desaturation + painful eye movements +	AstraZeneca (ChAdOx1)	1st	14d	Brain MRI: multiple T2/ FLAIR hyperintense lesions involving the subcortical white matter, posterior limb of bilateral internal capsules, pons and left middle cerebellar peduncle. The largest	CSF: a normal protein of 0.4 g/L (0.19 – 0.56 g/L), glucose of 4.8 mmol/L (2.8 – 4.5 mmol/L) with pleocytosis (white cell count 59 × 106/L) (<5 × 106/L) + CSF IgG was 0.06 g/L (<0.03 g/L) with serum IgG of 12.4 g/L (7.0 – 16 g/L) + oligoclonal	Serum myelin oligodendrocyte glycoprotein antibody (MOG) = negative	NR	MPS	Improvement in vision and discharged, repeat MRI Brain showed further improvement, visual evoked potentials showed improvement, no

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Table 1 (*continued*)

First author	Country	Age	Sex	Neurological symptoms	Type of COVID-19 vaccine	Dosage of COVID-19 vaccine	Time interval between vaccination and neurological symptoms	MRI results	CSF findings	Auto-antibodies	SARS-CoV-2 PCR	Treatment	Outcome
				fatigue + painful eye movements				lesion was in the right frontal centrum semiovale measuring 17 × 17 mm with multiple internal punctate foci of gadolinium contrast enhancement + There was no callosal involvement. Notably, there was no definite abnormal signal or enhancement of optic nerves / Spine MRI: evidence of demyelinating disease	IgG bands were present / Serum and CSF aquaporin 4 antibodies = negative				new symptoms to suggest a clinical relapse, consistent with a monophasic illness.
Netravathi et al. 2022	India	54	Female	Progressive quadriparesis + altered sensorium + drowsiness	AstraZeneca (ChAdOx1)	1st	14d	Brain MRI: T2/FLAIR hyperintensities in the corpus callosum, bl periventricular and subcortical white matter, infratentorial region with patchy contrast enhancement	CSF: 8 cells- lymphocytic predominant, Protein:77 mg/dl, Glucos:98 mg/dl	ANA, ANCA, CRP -negative Serum NMO-MOG = negative	NR	MPS + PE + Prednisolone	Significant improvement
		35	Female	Progressive paraparesis + altered sensorium + conscious + confused + paraparesis	AstraZeneca (ChAdOx1)	1st	9d	MRI: T2/FLAIR hyperintensities in mid brain, pons, left MCP, bl posterior internal capsule, thalamus, bl centrum semiovale and LETM from cervical cord to conus	CSF: 58 cells -lymphocytes P: 47.4 mg/dl, G: 106 mg/dl	ANA profile, ANCA, VDRL, RA factor = negative / serum MOG = positive / VEP, BERA, SSEP = normal	NR	MPS + Prednisolone	Significant improvement
		20	Female	Paraesthesias + paraparesis + altered sensorium	Covaxin (BBV152)	1st	1d	MRI: few juxtacortical and short segment cervical T2/FLAIR hyperintensity at C5 level with subtle enhancement	CSF: 8 cells + lymphocytic predominant, P:24.9 mg/dl, G:61 mg/dl	ANA profile, ANCA, VDRL, RA factor, CRP = negative / Serum and CSF NMO-MOG = negative / CSF OCB = Positive / VEP, BERA, SSEP = normal	NR	MPS + PE + Prednisolone	Significant improvement
		33	Female	Fever + vomiting + altered sensorium + persistent paraesthesias	AstraZeneca (ChAdOx1)	1st	14d	Brian MRI: T2/FLAIR hyperintensity in Bl fronto parietal region, no enhancement	CSF: 105 cells + lymphocytic predominant, P: 28.12 mg/dl, G: 70.4 mg/dl	Serum MOG = Strongly positive	NR	Acyclovir + MPS + Prednisolone	Significant improvement
		60	Male	Tingling paraesthesias + motor weakness + behavioural and memory disturbances	AstraZeneca (ChAdOx1)	2nd	14d	Brain MRI: multiple focal lesions in right pons, midbrain, medial temporal lobes, splenium of corpus callosum, high parietal lobe with tumefaction and peripheral enhancement	CSF: 9 cells – 90 % lymphocytes, P:68.3 mg/dl, G:132 mg/dl, OCBs-negative	ANA,ANCA,B12, Homocysteine,VDRL = negative / ACE = normal / Serum NMO and MOG = negative / VEP = normal	NR	MPS + Prednisolone	Significant improvement

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Table 1 (*continued*)

First author	Country	Age	Sex	Neurological symptoms	Type of COVID-19 vaccine	Dosage of COVID-19 vaccine	Time interval between vaccination and neurological symptoms	MRI results	CSF findings	Auto-antibodies	SARS-CoV-2 PCR	Treatment	Outcome
		45	Male	Fever + urinary retention + difficulty in walking	AstraZeneca (ChAdOx1)	1st	10d	Brain and spine MRI: hyperintensities in brainstem, cervicodorsal cord and supratentorial regions with central cord swelling	CSF: 44 cells – 44 % lymphocytes, P:90.9 mg/dl, G:68 mg/dl + rabies CSF PCR = Negative	VEP-l-141,R-129,BERA = normal / N20 = normal / P37–40 (mildly prolonged), ANA-U1RNP-1+,C-ANCA-, Serum MOG = strongly positive / S. NMO = Negative	NR	MPS + PE + cycles tab WYSOLONE + MG tab	Significant improvement
		52	Female	Progressive slurring of speech + muscle weakness + swallowing difficulty	AstraZeneca (ChAdOx1)	1st	35d	Brain MRI: tumefactive demyelination in left frontal hemisphere with insular involvement along with left more than right midbrain involvement	CSF: 2 CELLS,P-40.5 mg/dl,G-56 mg/dl ESR-18	ANA, ANCA = Negative / VDRL = Negative / S. NMO and MOG = Negative	NR	Rituximab + cycles Tab Wysolone + PE	Remained critically ill, requiring invasive ventilation, and died (after a prolonged intensive care unit stay and superimposed infection)
Permezel et al. 2021	Australia	63	Male	Vertigo + abdominal pain + fatigue + ketoacidosis + silent myocardial infarction + declining cognition + emerging disorientation + impaired attention	AstraZeneca (ChAdOx1)	1st	12d	Brain and cervical spine MRI: numerous bilateral foci (>20) of high T2 and FLAIR signal in the cerebral white matter, with both periventricular and juxtacortical involvement	NR	NR	NR	Empiric antibiotics + antivirals + corticosteroids + PE	MRI brain was repeated on day 19 and demonstrated no changes, and died on day 20 of admission.
Rinaldi et al. 2021	Italy	45	Male	Numbness + reduced visual acuity + dysarthria + dysphagia + clumsy right hand movements + urge incontinence	AstraZeneca (ChAdOx1)	1st	12d	Brian MRI: large, poorly marginated T2-weighted hyperintensities in the pons (which appeared swollen), right cerebellar peduncle, right thalamus, and multiple spinal cord segments (at the cervical, dorsal, and conus medullaris level). All lesions, except the thalamic one and a single dorsal spinal area, showed blurred gadolinium enhancement on T1-weighted images	CSF: mild lymphocytosis (44 leucocytes, 98 % mononuclear cells), normal proteins, no evidence of tumor cells on CSF cytology / CSF immunoelectrophoresis: the presence of three oligoclonal bands, with normal Link's Index / Extensive panel for onco-neural antibodies on serum and CSF = negative	Anti-aquaporin-4 (AQP4), anti-myelin oligodendrocyte glycoprotein (MOG) antibodies, anti-nuclear, anti-extractable nuclear antigens, anti-neutrophil cytoplasmic, and anti-cardiolipin antibodies = all Negative	NR	MPS + prednisone	Clinically improved in a few days, and MRI significantly improved
Shimizu et al. 2021	Japan	88	Female	Impaired consciousness +	Pfizer (BioNTech)	2nd	29d	Brian MRI: signal abnormalities in the	CSF: bacterial and fungal cultures, a CSF oligoclonal band screen, and a test for	antinuclear-, autoimmune vasculitis-, onconeural-, and anti-	NR	MPS	Impaired consciousness and gaze-evoked

(*continued on next page*)

Table 1 (*continued*)

First author	Country	Age	Sex	Neurological symptoms	Type of COVID-19 vaccine	Dosage of COVID-19 vaccine	Time interval between vaccination and neurological symptoms	MRI results	CSF findings	Auto-antibodies	SARS-CoV-2 PCR	Treatment	Outcome
				gaze-evoked nystagmus				bilateral middle cerebellar peduncles	autoantibodies against myelin basic protein = all negative	ganglioside antibodies = all negative			nystagmus were found to improve, further MRI brain scans revealed the signal abnormalities had decreased (Complete clinical recovery)
Simone et al. 2021	Italy	51	Female	Acute urinary retention + bilateral hypoesthesia	NR	NR	2w (14d)	MRI: enhancing T2 hyperintense lesions in the spinal cord with longitudinal extension, in the midbrain and in the optic nerves bilaterally	CSF: lymphocyte pleocytosis (50 cells/μL), negative oligoclonal bands	anti-MOG-IgG antibody = positive	Negative	MPS	Clinical improvement
Vogrig et al. 2021	Italy	56	Female	Unsteadiness of gait + clumsiness of left arm + malaise + chills + diplopia + mild ataxia + left-ward deviation of gait + urinary retention	Pfizer (BioNTech)	1st	2w (14d)	Brain MRI: an area of hyperintensity on fluid attenuated inversion recovery (FLAIR) sequences involving the left cerebellar peduncle, with modest mass effect on the fourth ventricle, which was not present on the previous MRI examination. No contrast enhancement was observed and the lesion did not exhibit diffusion restriction. In addition, new supratentorial areas of hyperintensity on FLAIR sequences were observed, the largest in the left centrum semiovale (unremarkable)	CSF: pleocytosis (80 cells/mm3), protein and glucose levels = normal	MOG, AQP4, GM1, GM2, GM3, GM4, GD1a, GD1b, GD2, GD3, GT1a, GT1b, GQ1b = all negative	Negative	Prednisone	Spontaneously recovered and underwent regular follow-up
Yazdanpanah et al. 2022	Iran	37	Male	Muscle weakness + dysphagia + drooling + nausea + vomiting + bilateral facial nerve paralysis	Sinopharm	1st	1 month (30d)	Brain MRI: typical imaging findings which presented as multifocal T2-FLAIR signal changes in the corticospinal tract, pons, and temporal lobe with diffusion restriction.	CSF: 2 WBCs, 32 RBCs, 56 mg/dL protein, and glucose of 97 mg/dL + IgG oligoclonal bands = negative	NR	Negative	PE + IVIG + antibiotic therapy + Heparin + Pantoprazole + Clindamycin + Paracetamol + MPS	Showed progressive recovery of motor function, and discharged (with an excellent general condition)

PE: Plasma exchane, MPS: Methylprednisolone, IVIG: Intravenous immuneglobulin, IVMP: IV methylprednisolone, NR: Not reported.

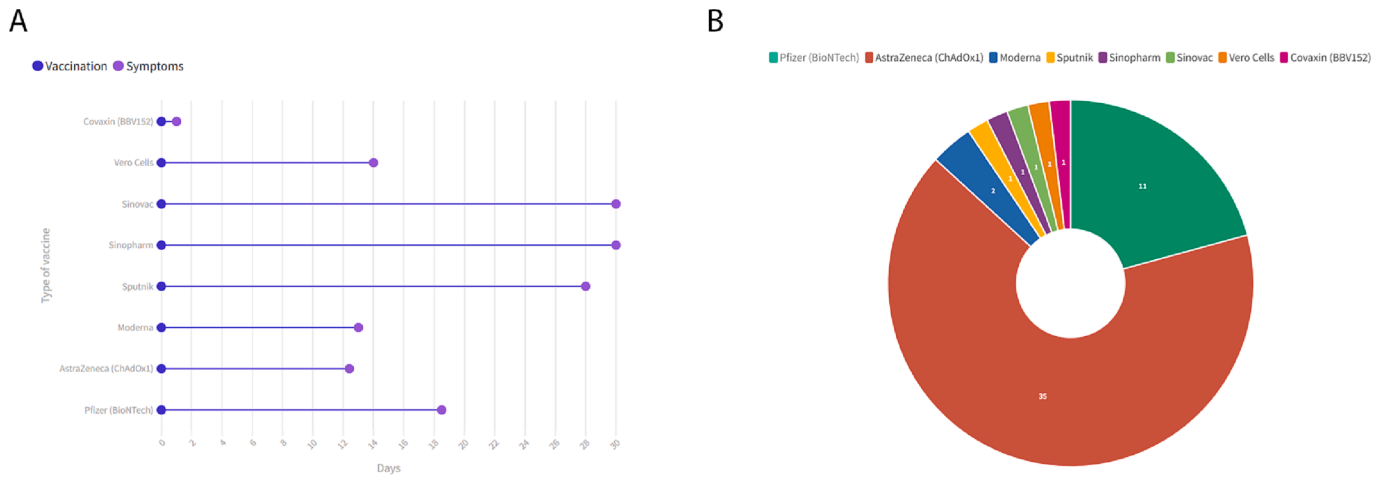

Fig. 2. The mean duration between vaccination and neurological symptoms on type of vaccine (A), and type of COVID-19 vaccine used among cases (B).

abstract evaluation. Finally, after the full-text screening, 20 studies with a total of 54 cases were entered into our systematic review [6,18,20–23,26–39].

Of the 54 ADEM cases with a mean age of 43.1 ± 15.7 and range [19–88], 33 patients (61.1 %) were female and 21 patients (38.8 %) were male (Table 1). There was no pediatric case of ADEM among included studies. Patients were originally from India (n = 10), Italy (n = 4), Germany (n = 3), Australia (n = 2), Japan (n = 2), USA (n = 2), Saudi Arabia (n = 1), Argentina (n = 1), UK (n = 1), China (n = 1), Poland (n = 1), Iran (n = 1), and Turkey (n = 1). Thirty-five patients received AstraZeneca (ChAdOx1), 11 Pfizer (BioNTech), two Moderna, and one each received Sinopharm, Sputnik, Sinovac, Vero Cells, and Covaxin (BBV152). The type of vaccine was not reported for one patient [35]. Among included patients, 45 (85.1 %) developed ADEM after the first dose of the COVID-19 vaccine, and seven (12.9 %) cases experienced ADEM after the second dose. The median time interval between vaccination and neurological symptoms was 14 days which ranged from 12 h to 63 days (Fig. 2). Twelve (22.2 %) patients experienced symptoms of muscle weakness, ten (18.5 %) presented unconsciousness, nine (16.6 %) patients had urinary complaints, nine (16.6 %) had visual impairments, and five (9.2 %) experienced a seizure. Most of the studies performed serological tests. anti-MOG antibody was positive in CSF of 16 (29.6 %) cases and antinuclear antibodies (ANA) were positive only in one (1.8 %) patient. Fifty-one (94.4 %) of the included patients received glucocorticoids, 18 (33.3 %) underwent plasmapheresis, and 11 received IVIg (20.3 %). After treatments, four (13.8 %) patients died. Forty-six patients had clinical improvement (85.1 %), also improvement in brain MRI was observed among 44 (81.4 %) patients. The full clinical, serological, and imaging findings are detailed in Table 1.

The result of the quality assessment revealed that 15 studies scored more than seven, and five studies scored below 6 (Table 2). The mean JBI score for all included studies was 7.15.

4. Discussion

Since the development of SARS-CoV-2 vaccines, several reports have noted the occurrence of ADEM after immunization. In the present study, we systematically collected a total of 54 reported cases of ADEM post-COVID-19 vaccination with the aim of reviewing clinical presentations, diagnostic features, therapeutic modalities, and final outcomes.

Generally, ADEM is a rare condition, which commonly occurred after a lag time of a few days to a mean of 26 days from a preceding infectious illness or immunization [40,41]. The main presentations include the acute onset of polyfocal neurologic symptoms together with encephalopathy, often with subsequent rapid worsening which leads to hospitalization. Affected patients present with motor deficits involving a single limb or result in paraparesis or quadriparesis. Likewise, sensory deficits are common, and frequent brainstem involvements lead to oculomotor dysfunction and dysarthria. Further presentations may include headache, malaise, meningismus, ataxia, seizure, aphasia, optic neuritis, nystagmus, extrapyramidal movement disorders, urinary retention, and increased intracranial pressure, which could be simply determined by localization of the lesions [42,43]. The lesions of ADEM are large, bilateral, and asymmetric which are poorly marinated, and could be observed as hyperintense lesions on T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences [44].

There are no pre-specified biomarkers or confirmatory tests for establishing the diagnosis of ADEM. Thus, ADEM is considered a diagnosis of exclusion, and other inflammatory and demyelinating disorders should be ruled out before confirmation of ADAM diagnosis. It would be worth noting that ADEM is more common in children and diagnostic criteria have been purposed for children with the main two presentations of multifocal central nervous system symptoms and polyneuropathy [45]. For adults, there are no consensus diagnostic criteria yet and unlike for children, evidence of neuropathy is not a required feature for diagnosis, suggesting incomplete presentations for adult patients.

Since ADEM is more common in children [46] and COVID-19 vaccination for young adults is in its early phase, there may be a probability of an increased number of ADEM cases in the following months. Furthermore, ADEM represents a monophasic nature most frequently. Antibodies developed against MOG protein are a potential marker for the evolution of ADEM [47]. It has been reported that the risk of MOG-seropositive and further episodes of relapse is considerably higher in children [48,49]. As a result, the vaccination of young individuals must be performed with strict supporting neurologic surveillance to detect ADEM cases more rapidly and cure them more efficiently.

Apart from the occurrence of ADEM after vaccination, a number of cases have been diagnosed as ADEM post-SARS-CoV-2 infection. In a literature search that has been conducted by Etemadifar and colleagues, a total of 31 ADEM cases were identified following SARS-CoV-2 infection. The average age was 52.3 years with no gender predominance of cases (16 females and 15 males). Moreover, a reduced level of consciousness and GCS was evident in 55.8 % of patients, 35.4 % represented muscle weakness, and 12.9 % developed seizures. Also, the outcome of death was reported in 25 % of patients [50]. By contrast, our cohort of cases was younger (average 46.5 years of age) and females comprised 65.5 % of the total population. We found that post-vaccination ADEM represented muscle weakness, unconsciousness, and seizure in 31.0 %, 27.6 %, and 10.3 % of patients. Furthermore, the mortality rate was 13.8 % in our cases. As it is evident, the rate of

Table 2
The Joanna Briggs Institute Critical Appraisal tools for Case Reports.

	Al-Quliti et al. 2022	Ancau et al. 2021	Ballout et al. 2022	Francis et al. 2022	Cao et al. 2021	Ahmad et al. 2022	Kania et al. 2021	Kenangil et al. 2021	Lazaro et al. 2022	Maramattom et al. 2022	Miyamoto et al. 2022	Mumoli et al. 2021	Nagaratnam et al. 2022	Netravathi et al. 2022	Permezel et al. 2021	Rinaldi et al. 2021	Shimizu et al. 2021	Simone et al. 2021	Vogrig et al. 2021	Yazdanpanah et al. 2022
Were patient's demographic characteristics clearly described?	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Was the patient's history clearly described and presented as a timeline?	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	No
Was the current clinical condition of the patient on presentation clearly described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were diagnostic tests or assessment methods and the results clearly described?	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Was the intervention (s) or treatment procedure(s) clearly described?	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes
Was the post-intervention clinical condition clearly described?	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were adverse events (harms) or unanticipated events identified and described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Does the case report provide takeaway lessons?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Total rank	5	7	8	8	6	8	8	6	8	7	8	8	8	5	8	7	8	5	8	7

adverse events of ADEM following infection is higher than that that occurred post-vaccination. This could be potentially justified by the concomitant infection by SARS-CoV-2 which deteriorated the course of ADEM as compared to those who experienced ADEM after immunization with SARS-CoV-2 vaccines.

Interestingly, the plausibility of SARS-CoV-2 as a viral triggering for ADEM has been extended to other members of the coronaviridae family. In this regard, MERS and OC43 coronaviruses have also been linked to ADEM in recent years [51,52]. Growing evidence has been biologically postulated that the shared epitope between SARS-CoV-2 antigens and neuronal proteins may promote subsequent autoimmune responses against the central nervous system through molecular mimicry [53,54].

In addition to SARS-CoV-2 vaccines, there have been also some reports regarding the occurrence of ADEM following hepatitis, herpes papillomavirus (HPV), measles, mumps, and rubella (MMR), diphtheria, tetanus, and pertussis (DTAP), polio, and seasonal flu vaccines [55,56]. Analyzing the data from the Vaccine Adverse Event Reporting System (VAERS) database showed that vaccines against seasonal flu and HPV were most frequently associated with ADAM [57]. A mean number of 40 annual ADEM events following vaccination was reported from 2005 to 2012 in the VAERS database [57].

The challenging differential diagnosis spectrum of ADEM mostly consists of CNS inflammatory demyelinating disorders such as the first attack of multiple sclerosis, autoimmune encephalitis, neuromyelitis optica, infectious meningoencephalitis, Bickerstaff encephalitis, and transverse myelitis. The lack of oligoclonal bands restricted to the CSF, the absence of periventricular lesions, variations in clinical symptoms, and the clinical evolution of ADEM are not in favor of Multiple Sclerosis (MS), although requiring a long follow-up for ruling out the dissemination in time which is the core characteristic of MS [58]. In addition, memory impairments, seizures, and psychiatric symptoms along with the presence of autoantibodies which are the typical manifestations of autoimmune encephalitis are not common features in ADEM [59]. The MOG antibody–associated disorder (MOGAD) consists of ADEM, transverse myelitis, and optic neuritis. However, there is clinical overlap between MOGAD, MS, and NMOSD, patients with high titer of anti-MOG antibodies should not be diagnosed with MS or NMOSD [60]. Furthermore, 16 (29.6 %) of our included subjects were positive for anti-MOG antibodies. A study by Wendel et al. found that patients with declining anti-MOG antibodies have a significantly lower risk of relapse [61]. The pathognomonic feature of 40–90 % of cases of neuromyelitis optica depending on the demographic is the presence of disease-specific aquaporin-4 (AQP4) antibody, which plays a key role in the pathogenesis of the disease [62]. Also, 10–40 % of cases with negative AQP4 antibody have positive MOG antibody which is mostly present in ADEM [61]. Among included studies, two cases by Francis et al. reported being positive for AQP4 antibody [39]. Based on the new criteria, MOGAD is typically linked to acute disseminated encephalomyelitis, optic neuritis, or transverse myelitis, and is less frequently connected with cerebral cortical encephalitis, brainstem presentations, or cerebellar presentations. MOGAD may manifest as either a monophasic or relapsing disease course, and diagnostic accuracy relies on the use of MOG-IgG cell-based assays [62]. It is essential to exclude diagnoses such as multiple sclerosis, although not all patients with multiple sclerosis require screening for MOG-IgG [62]. In differentiating the diagnosis of ADEM from infectious meningoencephalitis, evidence of meningismus together with the examination of CSF cytology and PCR might be helpful. Furthermore, Bickerstaff encephalitis and post-infection transverse myelitis are considered subtypes of ADEM, in which demyelination and inflammation are confined to the brainstem and spinal cord, respectively [56]. Therefore, in the era of the COVID-19 pandemic considering the sign and symptoms of systemic inflammation like a fever that occurred following SARS-CoV-2 infection or vaccination in conjunction with multifocal neurologic symptoms could confirm the diagnosis of ADEM.

Our study is the most up-to-date systematic review regarding clinical presentations, CSF findings, imagining information, and treatment outcomes of patients with ADEM after COVID-19 vaccination. Nevertheless, some limitations should be considered when interpreting our findings. Firstly, the lack of standard criteria for diagnosis of ADEM in adult patients may result in the variety of case definitions among our included patients. Secondly, incomplete data were reported for some variables which distorted making a comprehensive conclusion. Thirdly, the need for rapid reporting of the vaccine-associated adverse events led to the publication of studies with truncated follow-up duration which resulted in unknown information about the long-term consequences of the disease and the probable risk of relapse after a partial remitting.

In conclusion, it is not clear that ADEM could be a potential complication of COVID-19 vaccination based on the current evidence. However, this rare condition should not trigger stopping the mass vaccination programs and vaccine hesitancy since the only way to eradicate the current pandemic of COVID-19 is to extend the number of immunized people. Considering the causal and temporal association between SARS-CoV-2 vaccination and the occurrence of ADEM, neurologists must be aware of the serious neurological consequences that may arise after COVID-19 immunization in particular for the ChAdOx1 vaccine, and take immediate measures to avoid severe outcomes. Moreover, providing an integrated registry system for gathering detailed information on ADEM cases is highly recommended in order to report the cases in a standardized manner from all over the world.

5. Consent for publication

This manuscript has been approved for publication by all authors.

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Ethical approval

No need.

Author contributions

FN, MN, and HH: Designed the study and wrote the paper; FN and SHR: collected data, analyzed and interpreted the data, and wrote the draft version of the manuscript. The manuscript was revised and approved by all authors.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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